EDITORIAL

Reducing Mortality Due to Cervical Cancer

PAPNET Fails the Test

SINCE ITS INTRODUCTION into clinical practice in the 1940s, the Papanicolaou smear has become one of the most notable success stories in preventive screening. The overall impact of regular screening in an organized program is a reduction of the number of women in whom invasive cervical cancer develops of up to 90%.[1]

Despite this success, concerns remain about the weaknesses inherent in Papanicolaou smear testing. The weakness of greatest concern to clinicians and women is the potential for a false-negative result. Sources of a false-negative result include failure of the clinician to obtain an adequate sample, failure of the cytopathology laboratory to read the slide accurately, and chance errors in sampling, which will continue to occur even with the most carefully applied sampling techniques. There have been efforts to increase the ability of the clinician to obtain an adequate sample (by use of tools such as the Cytobrush [Med Scand, Malmö, Sweden] and Ayre spatula or Cervex brush [Med Scand, Hollywood, Fla]),[2,3] and to improve the reliability of cytopathology laboratories through quality assurance regulations and standardized terms for describing findings.[4,5]

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Given these efforts, there remains a divergence of opinion as to the sensitivity of Papanicolaou testing and the risk for a false-negative test result. The reported range has varied from 5% to 25%. False-negative rates are likely to be at the lower end of the range when appropriate measures are used to obtain and to read a sample.[6] False-negative rates are further reduced in organized screening programs with repeated screening. The long-term course of cervical squamous cell abnormalities preceding invasive cervical cancer provides the opportunity for detection of abnormalities missed on results of an initial smear in the second or third round of screening. With repeated screening, the performance of cervical cytologic screening is best, and false-negative rates may be reduced by 80% after 3 consecutive smears with negative findings.[1] Nevertheless, there remains a climate of fear of clinical and legal consequences should any abnormality on results of cervical cytologic screening be overlooked.

The past 20 years have brought the introduction of many technologies that have attempted to improve the diagnosis of cervical cancer and its precursors. These have included colposcopy, cervicography, speculoscopy, new cytologic sampling instruments (Cytobrush, Cervex Brush), new methods for processing the cytologic sample (Thinprep; Cytec, Boxborough, Mass), and methods for review of cytologic interpretation (PAPNET [Neuromedical Systems, Incorporated, Suffern, NY], Neopath [Redmond, Wash]). Many of these tests, including PAPNET, have been designed specifically to reduce the rate of false-negative results. PAPNET, based on computerized imaging and neural network artificial intelligence, has been approved by the US Food and Drug Administration for rescreening of Papanicolaou smears with findings interpreted as negative by cytotechnologists. Would the widespread use of PAPNET result in tangible benefits to our patients? What are the drawbacks? What are the costs?

Brotzman et al[7] sought to answer some of these questions in this issue of the ARCHIVES. They conducted a prospective evaluation of PAPNET rescreening of 1200 Papanicolaou smears with initial negative findings in a community hospital setting. The most important findings of this study are as follows:

1. Of 1200 smears with findings initially interpreted as negative by cytotechnologists, PAPNET identified 37 as requiring additional review. Subsequent review of these by a pathologist identified 8 cases of atypical squamous cells of undetermined significance (ASCUS). No cases of squamous intraepithelial lesions (SIL) or cervical cancer were identified.

2. In 13 months of follow-up, of the 8 patients with ASCUS, 6 underwent follow-up studies. Results of 3 were negative; 1 repeated smear showed low-grade SIL; and 2 repeated smears showed ASCUS.

3. The estimated marginal cost of PAPNET review in this laboratory, compared with 100% manual rescreening by a cytotechnologist of all smears with negative findings, ranged from $7832 to $35 379 per case of ASCUS detected.

O'Leary et al[8] from the Armed Forces Institute of Pathology corroborated these findings in another setting. A total of 5478 Papanicolaou smears randomly selected for manual rescreening and with findings interpreted as negative or showing benign cellular changes underwent rescreening with PAPNET. PAPNET required additional review of 29% of the slides.

Eleven of these were referred to a consensus panel of 3 pathologists and 3 cytotechnologists for review. Ultimately, 5 cases of ASCUS and 1 case of atypical glandular cells of undetermined significance were identified. Low-grade SIL ultimately developed in 1 of these patients, as seen on results of a follow-up Papanicolaou smear. Estimated costs per additional case of ASCUS or atypical glandular cells of undetermined significance detected were $5825 to $33 781, compared with 100% manual rescreening.

In summary, findings from both studies indicate that the addition of PAPNET to routine cervical cytologic screening is unlikely to detect significant lesions with any frequency, and that at current costs, manual rescreening is substantially less expensive. Despite these consistent findings from large, well-designed studies, the pressure on clinicians and on cytopathology laboratories to avoid false-negative results at all costs looms large. This pressure recently has included direct consumer advertising from Neuromedical Systems, Incorporated.

The history of technology in medical practice is replete with methods disseminated widely into practice based on initially promising results that were withdrawn when rigorous evaluation showed no significant benefit.[9,10] Present evidence indicates that automated rescreening in general will add little to the effectiveness of a good community laboratory. If the costs become less than those of manual rescreening, automated rescreening may become a useful part of cytology laboratory quality control.

Presently in the United States, 25% of women have not had a Papanicolaou smear in the past 3 years.[11] Percentages are higher among low-income and uninsured women.[12] Lack of follow-up after an abnormal result may be as high as 40% to 50%.[13] Programs to reach women who have not undergone screening and to improve follow-up after abnormal results will reduce mortality and morbidity from cervical cancer more effectively than will costly efforts to apply technology to eliminate false-negative results.

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Clinical Pearl

Herpes Simplex Causes Bell Palsy

Herpes simplex virus type 1 genomes were found in 4/5 patients with Bell palsy. (*Ann Intern Med.* 1996;124:27-30.)